REMARKS

Status of the Claims

Claims 1-8, and 9-21 are pending. Claims 1-3, and 6-8 are amended. Claims 17-21 are added.

No new matter is added in the above claims. Applicants respectfully submit that claims 19-21, are clearly supported in the specification through express, implicit, or inherent disclosure, since one of ordinary skill in the art would immediately recognize the structure as being amphotericin B.

Issues Under 35 U.S.C. § 102 and 103

Claims 1-10, and 12-16 are rejected under 35 U.S.C. § 102, as allegedly being anticipated by, or in the alternative, obvious over U.S. Patent 4,663,167 to Lopez-Berstein et al. This rejection is respectfully traversed. With respect to claims 9-10 and 12-16, this rejection is moot in view of their cancellation in the above amendment. With respect to claims 1-8, reconsideration and withdrawal thereof of this rejection are requested.

As stated in the specification, impurity issues have serious implications on the toxicity of amphotericin B during treatment of fungal infections in humans. These impurities contribute to side effects that include severe flu-like symptoms, capillary leak, pulmonary congestion, etc.

Through a novel purification method, the present inventors have an improved

composition that allows a much more isolated amphotericin B product. These compositions have a much higher amphotericin B content than prior art compositions – thus being a purer composition in the context of the present invention. Table 2 in the specification shows the amphotericin B content for several prior art compositions.

The compositions of the present invention, which have a high amphotericin B content and a low impurity content, greatly reduce the toxicity of standard amphotericin B treatment. The compositions of the present invention are substantially free from polyene contaminants such as amphotericin A, and endotoxins – sources of the side effects mentioned above and in the specification.

Amphotericins are insoluble in aqueous solution. Consequently, they are commonly supplied commercially as a combination of amphotericin B, lipid carriers, desoxycholate and/or buffers, and the contaminants described above. US '167 is directed to treating a fungal infection with amphotericin B encapsulated in an allegedly improved lipid carrier, a substantially sterol-free liposome. US '167 is discussed in paragraph 33 (as published) of the instant application as describing a suitable delivery method of the present invention.

However, US '167 fails to disclose or suggest the claimed purity features. In fact, this reference fails to even address amphotericin B purity in the same sense. On the other hand, US '167 is concerned with encapsulation. At col. 4, lines 8-19, achieving 100% encapsulation is discussed.

In order to anticipate a claim, each and every element as set forth in the claim must be described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). Applicants respectfully submit that in view of the deficiencies discussed above, it is clear that US '167 does not anticipate the present invention.

Additionally, with respect to obviousness, Applicants respectfully submit that since US' 167 is silent as to the claimed features, there can be no suggestion to modify US '167 to arrive at the present invention. In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings to arrive at the present invention with a reasonable expectation of success. The prior art reference (or references when combined) must also teach or suggest all the claim limitations. See M.P.E.P. §2142.

Accordingly, since US '167 fails to anticipate or render obvious the rejected claims, Applicants respectfully request that this rejection be withdrawn.

Claims 1-10 and 12-16 are rejected under 35 U.S.C. § 103 as allegedly being obvious over US '167 in view of US Patent No. 4,902,789 to Michel et al. or US Patent No. 4,308,375 to

Tsang. This rejection is respectfully traversed. With respect to claims 9-10 and 12-16, this rejection is moot in view of their cancellation in the above amendment. With respect to claims 1-8, reconsideration and withdrawal thereof of this rejection are requested.

The deficiencies of US '167 are discussed above. These deficiencies are not remedied by the secondary references.

US '789 discloses a four solvent system for purifying amphotericin B: methanol, dimethylformamide, methylene chloride, and water. However, purity is measured as a "residue on ignition" as a weight percent (vs. a percentage of impurities for the present invention). It is difficult to extrapolate purity as measured by residue on ignition to the present application because many of the contaminants the present inventors identified as polyenes should still be present based on the residue on ignition measurement. In addition, the most toxic contaminant, endotoxin, should also leave little residue upon ignition. Accordingly, endotoxin contamination was not assessed in US '789. The assessment of purity based on chemical property of the agent is not desirable. The use of highly sensitive and specific techniques (high pressure liquid chromatography or gas chromatography) is the industry standard for agents used in humans. Tremendous amounts of contaminant with similar "melting points" or "ignition points" could be present in a final product that one would not want administered as a medicament.

Likewise, the other secondary reference, US '375, fails to remedy the deficiencies of the primary reference. This patent discloses a method of purifying amphotericin B with an ion

exchange column, removing gram positive and gram negative bacteria. From a review of this reference, Applicants respectfully submit that the disclosed process would not result in the features claimed. In fact, Applicants respectfully submit that the US '375 process, like the other discussed above, does not address the amphotericin B formulation claimed.

In view of the above, Applicants request that this rejection be withdrawn.

Claim 11 is rejected under 35 U.S.C. § 103 as allegedly being obvious over US '167 in view of an assortment of secondary references. This rejection is respectfully traversed, but is moot in view of the cancellation of claim 11.

Petition for an Extension of Time

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants hereby petition for a three-month extension of time for filing a response to the outstanding Office Action. Payment for the extension of time fee is being submitted with the electronic filing of this response. You are authorized to charge any deficiency or credit any overpayment associated with the filing of this application to Deposit Account 50-2752.

Finally, please contact the undersigned if there are any questions regarding this Amendment or the application in general.

Respectfully submitted,

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